

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | |
|--|-----------|--|
| (51) International Patent Classification ⁶ : A61K 31/05, 9/107, 47/24, 47/28 | A1 | (11) International Publication Number: WO 98/53805 (43) International Publication Date: 3 December 1998 (03.12.98) |
| (21) International Application Number: PCT/EP98/03004 (22) International Filing Date: 14 May 1998 (14.05.98) (30) Priority Data: 1224/97 26 May 1997 (26.05.97) CH (71) Applicant (for all designated States except US): SAUCY LIMITED [IE/IE]; 20 Clanwilliam Terrace, Dublin 2 (IE). (72) Inventor; and (75) Inventor/Applicant (for US only): DE TOMMASO, Vincenzo [IT/IT]; Residenza Alberata, 352, I-20089 Basiglio (IT). (74) Agents: DRAGOTTI, Gianfranco et al.; Dragotti & Associati S.r.l., Galleria San Babila, 4/D, I-20122 Milano (IT). | | (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> |
| (54) Title: CLEAR, INJECTABLE FORMULATION OF AN ANESTHETIC COMPOUND (57) Abstract <p>Aqueous, injectable pharmaceutical formulation comprising propofol, a pharmaceutically acceptable salt of a bile acid and a lecithin.</p> | | |

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|----|--------------------------|----|--|----|--|----|--------------------------|
| AL | Albania | ES | Spain | LS | Lesotho | SI | Slovenia |
| AM | Armenia | FI | Finland | LT | Lithuania | SK | Slovakia |
| AT | Austria | FR | France | LU | Luxembourg | SN | Senegal |
| AU | Australia | GA | Gabon | LV | Latvia | SZ | Swaziland |
| AZ | Azerbaijan | GB | United Kingdom | MC | Monaco | TD | Chad |
| BA | Bosnia and Herzegovina | GE | Georgia | MD | Republic of Moldova | TG | Togo |
| BB | Barbados | GH | Ghana | MG | Madagascar | TJ | Tajikistan |
| BE | Belgium | GN | Guinea | MK | The former Yugoslav Republic of Macedonia | TM | Turkmenistan |
| BF | Burkina Faso | GR | Greece | ML | Mali | TR | Turkey |
| BG | Bulgaria | HU | Hungary | MN | Mongolia | TT | Trinidad and Tobago |
| BJ | Benin | IE | Ireland | MR | Mauritania | UA | Ukraine |
| BR | Brazil | IL | Israel | MW | Malawi | UG | Uganda |
| BY | Belarus | IS | Iceland | MX | Mexico | US | United States of America |
| CA | Canada | IT | Italy | NE | Niger | UZ | Uzbekistan |
| CF | Central African Republic | JP | Japan | NL | Netherlands | VN | Viet Nam |
| CG | Congo | KE | Kenya | NO | Norway | YU | Yugoslavia |
| CH | Switzerland | KG | Kyrgyzstan | NZ | New Zealand | ZW | Zimbabwe |
| CI | Côte d'Ivoire | KP | Democratic People's Republic of Korea | PL | Poland | | |
| CM | Cameroon | KR | Republic of Korea | PT | Portugal | | |
| CN | China | KZ | Kazakhstan | RO | Romania | | |
| CU | Cuba | LC | Saint Lucia | RU | Russian Federation | | |
| CZ | Czech Republic | LI | Liechtenstein | SD | Sudan | | |
| DE | Germany | LK | Sri Lanka | SE | Sweden | | |
| DK | Denmark | LR | Liberia | SG | Singapore | | |
| EE | Estonia | | | | | | |

CLEAR, INJECTABLE FORMULATION OF AN ANESTHETIC COMPOUND

The present invention relates to a clear, injectable, pharmaceutical formulation of propofol.

Propofol, whose chemical name is 2,6-bis-(1-methylethyl)phenol, is a known anaesthetic, largely used for general anaesthesia.

The propofol formulation which is present on the market is a non-transparent, white, oil-in-water emulsion. Similar formulations are described for example in US 4,798,846 and in GB 2,298,789.

Other injectable propofol preparations have been described. More particularly, WO 96/32135 discloses a pharmaceutical composition in which propofol is used as an inclusion complex with 2-hydroxypropyl- β -cyclodextrine while WO 97/10814 discloses the use of nanodispersions of propofol to be administered by intravenous route.

It has now been found that a transparent injectable formulation of propofol may be obtained by mixing said propofol with a bile acid and with a lecithin. More particularly, said formulation presents noteworthy advantages in respect of the presently marketed formulation. Such a formulation is clear, and, hence, the presence of foreign particles, such as glass residues, fibers, undissolved substances and the like, inside the vials or bottles can be easily controlled. This feature is very important for the product safety because, in general, the ready-for-use injectable solutions and, with greater reason, those exclusively used by intravenous route, as is the case of propofol, must not contain any foreign particles.

Furthermore, the present injectable formulation may be diluted in most of the solutions for infusion, thus allowing the anaesthetist physician to dose the drug with better precision and to administer it with a greater regularity in order to obtain a more precise and safer effect.

Another very important advantage is the fact that the present formulation is stable within a temperature range from +2° to +35°C, which is broader than the stability temperature range (+2÷+25°C) of the presently marketed formulation. Moreover, the production of the formulation of the present invention does not require any particular or sophisticated apparatus, but it is sufficient to use a normal equipment for the production of pharmaceutical formulations for injectable use.

Thus, it is another object of the present invention to provide an aqueous, injectable pharmaceutical composition comprising:

- (a) propofol;
- (b) a pharmaceutically acceptable salt of a bile acid;
- (c) a lecithin.

The bile salt is advantageously selected from the group consisting of glycocholic acid, cholic acid, chenodesoxycholic acid, taurocholic acid, glycochenodesoxycholic acid, taurochenodesoxycholic acid, lithocholic acid, ursodesoxycholic acid, dehydrocholic acid, the preferred one being glycocholic acid.

The pharmaceutically acceptable salts of the bile acids may be advantageously selected from the group consisting of the sodium, potassium, calcium, magnesium or ammonium salts. The sodium salt being preferred.

Sodium glycocholate is the particularly preferred pharmaceutically acceptable salt of a bile acid.

A lecithin may be soybean lecithin or egg lecithin.

The use of a salt of a cholanic acid in admixture with lecithin for the preparation of mycellar solutions of non-steroidal anti-inflammatory compounds, in order to reduce or suppress the local irritations and the haemolytic effects deriving from the parenteral administration of aqueous solutions of said drugs, is described in EP-A-280887.

In the aqueous pharmaceutical formulation of the present invention, propofol is present in an amount of from 8 mg to 12 mg per 1 ml of solution, advantageously from 9 mg to 11 mg per ml of solution, preferably in an amount of 10 mg per ml of solution.

The pharmaceutically acceptable salt of the bile acid is present in said aqueous pharmaceutical formulation in an amount, referred to the free acid, of from 25 to 110 mg per 1 ml of solution, preferably of from 50 to 60 mg per ml of solution. Lecithin is present in an amount of from 40 to 150 mg, preferably of from 70 to 80 mg per ml of solution. Soybean lecithin is the preferred lecithin.

According to an advantageous embodiment of the present invention, the aqueous, injectable pharmaceutical composition comprises:

- from 8 to 12 mg of propofol;
- from 25 to 110 mg of a bile acid, as a pharmaceutically acceptable salt thereof;

- from 40 to 150 mg of a lecithin,
per ml of solution.

According to a particularly advantageous embodiment of the present invention, in this aqueous, injectable pharmaceutical composition, said bile acid salt is sodium glycolate and said lecithin is soybean lecithin.

An aqueous, injectable pharmaceutical formulation comprising from 8 to 12 mg, preferably 10 mg, of propofol per 1 ml of solution, from 50 to 60 mg of glycolic acid, as sodium glycolate, per ml of solution, and from 70 to 80 mg of soybean lecithin per ml of solution is particularly advantageous.

The water used in the present formulation is water for injectable preparations.

For the manufacture of the present pharmaceutical formulation, the bile acid salt may be straightforwardly used as starting material or the free acid may be previously salified with a suitable alkalinizing agent which may be, for example, an alkaline metal hydroxide such as sodium, potassium or lithium hydroxide, an alkaline-earth metal hydroxide, such as calcium or magnesium hydroxide, a metal oxide such as magnesium or aluminium oxide, a carbonic acid salt, such as sodium or potassium carbonate, sodium or potassium bicarbonate, a phosphoric acid salt, such as sodium, potassium or calcium phosphate, for example trisodium phosphate.

It is another object of the present invention to provide a process for the preparation of an aqueous, injectable pharmaceutical composition as mentioned above, which comprises:

(a) adding lecithin to an aqueous solution of the pharmaceutically acceptable salt of the bile acid, said solution having a pH of from 4.5 to 6.5;

(b) heating the aqueous dispersion to a temperature of from 35° to 85°C for 60 minutes;

(c) adding propofol, previously heated at a temperature of from 35° to 85°C, to the solution obtained in step (b), heated at a temperature of from 35° to 85°C;

(d) cooling and adding water to reach the final volume.

More particularly, the present invention concerns a process for the preparation of an aqueous, injectable pharmaceutical composition containing propofol, a pharmaceutically acceptable salt of a bile acid and a lecithin, as illustrated above, which comprises:

(a) adding lecithin to an aqueous solution of the pharmaceutically acceptable bile acid salt, said solution having a pH of from 4.5 to 6.5;

(b) heating the aqueous dispersion at a temperature of from 35° to 85°C until solution is complete;

(c) adding propofol, previously heated to the temperature of from 35° to 85°C, to said solution;

(d) cooling to room temperature and adding water until the final volume is reached;

all the steps being carried out in substantial absence of oxygen.

The expression "substantial absence of oxygen" means that the solution, during the process, should have a content of oxygen not higher than 1 part per million (p.p.m.), preferably not higher than 0.5 p.p.m.

As set forth above in step (a), the pharmaceutically acceptable salt of the bile acid, preferably sodium glycocholate, may be dissolved in water as such or prepared *in situ* by salification of the bile acid, preferably glycolic acid, with the selected base, preferably sodium hydroxide. In this latter case, the bile acid, preferably glycolic acid, is added to an aqueous solution of the base, preferably sodium hydroxide, by the adjusting the pH of the solution thus obtained with a pharmaceutically acceptable acid, preferably hydrochloric acid, in order to render said pH compatible with an intravenous administration. Said pH is kept at a value of from 4.5 to 6.5, advantageously from 5 to 6, preferably of about 5.5.

Step (a) is normally carried out at room temperature (20°±25°C), but a higher temperature, for example of about 30°C is also acceptable.

The medium is advantageously kept under substantial absence of oxygen by using any technique for removing it, for example by bubbling an inert gas, preferably nitrogen, in said medium and by keeping the medium under inert atmosphere throughout the process.

The content of oxygen may be measured according to known methods (for example using an oxygen-sensitive electrode) and kept not higher than 1 p.p.m., preferably lower than 0.5 p.p.m.

Lecithin, preferably soybean lecithin, is added under strong stirring, advantageously in an inert atmosphere, preferably under nitrogen stream.

In step (b), the mixture is heated at a temperature of from 35° to 85°C in order to obtain a complete dissolution.

Usually, a temperature of from 35° to 60°C, preferably of from 45° to 50°C, is used. Since bile acids and their salts are often surfactants, a foam may be obtained, which dissolves if the mixture is let to stand at rest, advantageously always in substantial absence of oxygen.

In step (c), to the solution thus obtained, heated to 35°÷85°C, preferably at 55°÷60°C, propofol, previously heated at the same temperature, is added under stirring and advantageously in an inert atmosphere, preferably under nitrogen stream.

In step (d) the clear solution thus obtained, if necessary homogenized, is cooled to room temperature (22÷25°C) and diluted with water until the desired volume is reached, preferably by keeping the oxygen concentration of the medium very low, advantageously not higher than 1 p.p.m., preferably lower than 0.5 p.p.m.

The solution thus obtained, when submitted to the conventional operations of pharmaceutical technique for the manufacture of injectable preparations, preferably kept in hermetically closed vessels, is ready for medical use.

Preferably, the formulation according to the present invention contains oxygen at a concentration not higher than 0.5 p.p.m.. In the vessel containing it (vial or bottle) the head space contains oxygen in an amount preferably not higher than 1%.

EXAMPLE

In a stainless steel reactor equipped with an heating shell, 186 ml of water for injectable preparation were introduced and nitrogen was bubbled therein to a concentration of dissolved oxygen lower than 0.5 p.p.m., by keeping the water temperature at about 25°C, then 4.8 g of sodium hydroxide were added therein, under gentle stirring and nitrogen stream. At complete dissolution, a control of the oxygen concentration, to be kept lower than 0.5 p.p.m., was made, then 54.6 g of glycocholic acid were quickly added in one portion by keeping the mixture at about 30°C under strong stirring and nitrogen atmosphere. After dissolution, the pH was in the range of 10÷12. After solubilization of the glycocholic acid, the pH was adjusted to 5.45÷5.5 with 1N hydrochloric acid, by adding said acid slowly and keeping the solution under strong stirring and nitrogen atmosphere (oxygen concentration lower than 0.5 p.p.m.) To the solution of sodium glycocholate, 75.6 g of soybean lecithin were slowly added, by keeping the solution under strong stirring and nitrogen

stream, then the suspension was heated at a temperature of $45\pm 50^{\circ}\text{C}$ under moderate stirring and nitrogen atmosphere until the formation of a great amount of foam was observed. The solution was cooled to room temperature and let to stand 18 hours under nitrogen pressure, whereafter the complete solubilization of the soybean lecithin was controlled. The solution was heated at $55\pm 60^{\circ}\text{C}$ and submitted for 10 minutes to the action of a homogenizer, under strong nitrogen stream. An amount of 10 g of propofol, previously heated to 60°C , was slowly poured into the previously obtained solution, by keeping it under homogenization and nitrogen stream, at a temperature of $65\pm 70^{\circ}\text{C}$. The solution was homogenized until a sample of solution, diluted 1:1 v/v with water for injectable preparations, resulted clear by naked eye. The solution was cooled to 25°C by adding 610 ml of water for injectable preparations, very slowly, into the solution at a temperature of 25°C with a content of dissolved oxygen lower than 0.5 p.p.m. Then the solution was kept under gentle stirring and nitrogen stream until the content of dissolved oxygen resulted lower than 0.5 p.p.m. Then, vacuum was made in the reactor in order to eliminate the gas dissolved in the solution and water for injectable preparation, with a content of dissolved oxygen lower than 0.5 p.p.m., was added to a volume of 1000 ml. The solution was kept under gentle stirring and nitrogen stream; the value of the pH was controlled in order to keep it at 6.0 ± 6.3 (if necessary, the value must be adjusted with 0.2% hydrochloric acid or with 0.2% sodium hydroxide). The amount of dissolved oxygen was controlled and the nitrogen bubbling was continued until an oxygen concentration lower than 0.5 p.p.m. was obtained. The solution was filtered in a sterile unit (class 100) through a 0.22-micron porous membrane, type Durapore[®] by Millipore, previously controlled and approved for its integrity. Vials or bottles were filled under nitrogen atmosphere, by controlling the amount of residual oxygen in the head space of the vial or bottle in order to keep it lower than 1%.

STABILITY ASSAYS

After the initial measurement (time 0 \equiv T₀) controls were made after 30 days (T₃₀) and after 60 days (T₆₀) from T₀.

For the detection of propofol, a method by HPLC performed with inverse phase column and a UV detector was set up. The specificity and response linearity study in the concentration range of the vials gave satisfactory results to perform the stability control suitably.

EXPERIMENTAL

MATERIALS AND METHODS

Reagents

- Acetonitrile for HPLC, Merck - Darmstadt
- Deionized water from equipment "Maxima ultra pure water", Elga
- Propofol Standard, Archimica - code 61005, batch No. 95005-0-01 (purity grade: 99.8%; density: 0.955 g/ml).

Standard Solutions

- Standard solution of propofol: in a 100-ml volumetric flask, about 20.0 mg, exactly weighed, of pure product are mixed with water to volume.
- Solutions of propofol samples in vials: the content of two vials are poured in a perfectly dried flask. 2 ml of the liquid of the vials are pipetted, by a glass pipette, poured in a 100-ml volumetric flask and brought to volume with water.

Equipment

- HPLC CM 4000, Milton Roy, equipped with
- valve Rheodyne 7125 with a 10- μ l loop;
- detector U.V. Spectromonitor 3100, Milton Roy, with variable wavelength;
- integrator Mega 2, Carlo Erba, with paper speed = 0.5 cm/min.;
- column: Lichrospher 100 RP-18 (125 cm x 4 mm i. d. - 5 μ particle size), Merck - Darmstadt;
- precolumn: RP 18, Merck - Darmstadt.

Chromatographic Conditions

- Mobile phase: acetonitrile/water = 60:40 v/v
- Flow: 1 ml/min.
- Detector wavelength: 270 nm.
- Average elution time of propofol: 4.30 ± 1.00 .

Analytical detection

For the detection of propofol concentration in the vials, the standard solution of propofol is analyzed by repeating the analysis four times. The solutions of propofol samples in vials are analyzed immediately after the detection of the standard, by repeating the analysis twice. From the comparison of the average areas drawn for the peaks of the propofol, the concentration in mg/ml of the active principle in the solution of the vials is calculated.

The results summarized in the table show that the solution object of the present patent application remains stable and clear for a period of at least 150 days from the preparation date, within a broad temperature range.

| PROPOFOL 10 mg/ml - Temperature: 5°C | | | | |
|---------------------------------------|------|------------------------|-------|------------------|
| ANALYSIS DATE | DAYS | CONCENTRATION mg/ml | pH | DEGRADATION % |
| 16.10.96 | 0 | 8.57 | 6.00 | 0 |
| 19.11.96 | 30 | 8.58 | 6.17 | + 0.12 |
| 17.12.96 | 60 | 8.62 | 6.12 | + 0.58 |
| 10.02.97 | 120 | 8.48 | n. d. | - 1.05 |
| 27.03.97 | 150 | 8.25 | 6.15 | -3.70 |
| PROPOFOL 10 mg/ml - Temperature: 25°C | | | | |
| ANALYSIS DATE | DAYS | CONCENTRATION mg/ml | pH | DEGRADATION % |
| 16.10.96 | 0 | 8.57 | 6.00 | 0 |
| 19.11.96 | 30 | 8.46 | 6.16 | - 1.28 |
| 17.12.96 | 60 | 8.38 | 6.13 | - 2.21 |
| 10.02.97 | 120 | n. d. | n. d. | n. d. |
| 27.03.97 | 150 | n. d. | n. d. | n. d. |
| PROPOFOL 10 mg/ml - Temperature: 40°C | | | | |
| ANALYSIS DATE | DAYS | CONCENTRATION mg/ml | pH | DEGRADATION % |
| 16.10.96 | 0 | 8.57 | 6.00 | 0 |
| 19.11.96 | 30 | 8.52 | 6.19 | - 0.58 |
| 17.12.96 | 60 | 8.38 | 6.15 | - 2.21 |
| 10.02.97 | 120 | 8.34 | 6.21 | - 2.68 |
| 27.03.97 | 150 | 8.26 | 6.19 | -3.60 |

n. d. = not determined

CLAIMS

1. Aqueous, injectable pharmaceutical composition comprising:
 - (a) propofol;
 - (b) a pharmaceutically acceptable salt of a bile acid;
 - (c) a lecithin.
2. Composition according to claim 1, comprising:
 - from 8 to 12 mg of propofol;
 - from 25 to 110 mg of a bile acid, as a pharmaceutically acceptable salt thereof;
 - from 40 to 150 mg of a lecithinper ml of solution.
3. Composition according to claim 1 or 2, in which the bile acid salt is the sodium salt.
4. Composition according to one of claims 1 to 3, in which the bile acid, as a pharmaceutically acceptable salt thereof, is sodium glycocholate.
5. Composition according to one of claims 1 to 4, in which the lecithin is soybean lecithin.
6. Composition according to one of claims 1 to 5, comprising from 8 to 12 mg of propofol, from 50 to 60 mg of glycocholic acid, as sodium glycocholate, and from 70 to 80 mg of soybean lecithin per ml of solution.
7. Composition according to claim 6, containing 10 mg of propofol per ml of solution.
8. Composition according to claim 1, containing from 9 to 11 mg of propofol per ml of solution.
9. Process for the preparation of the aqueous, injectable pharmaceutical composition of claim 1, which comprises:
 - (a) adding lecithin to an aqueous solution of the pharmaceutically acceptable salt of the bile acid, said solution having a pH of from 4.5 to 6.5;
 - (b) heating the aqueous dispersion at a temperature of from 35° to 85°C for 60 minutes;
 - (c) adding propofol, previously heated at a temperature of from 35° to 85°C, to the solution obtained in step (b) heated at a temperature of from 35° to 85°C;
 - (d) cooling and adding water to the final volume.
10. A process according to claim 9, which comprises:

- (a) adding the lecithin to an aqueous solution of the bile acid salt, said solution having a pH of from 4.5 to 6.5;
- (b) heating the aqueous dispersion at a temperature of from 35° to 85°C until the dissolution is complete;
- (c) adding propofol, previously heated to the temperature of from 35° to 85°C to said solution;
- (d) cooling to room temperature and adding water until the final volume is reached;

all the steps being carried out in substantial absence of oxygen.

11. A process according to claim 9 or 10, wherein the bile acid salt is sodium glycocholate.

12. A process according to claim 11, wherein sodium glycocholate is prepared *in situ*.

13. A process according to one of claims 9 to 12, in which the lecithin is soybean lecithin.

14. A process according to one of claims 10 to 13, in which the substantial absence of oxygen is obtained by bubbling an inert gas into the mixture.

15. A process according to claim 14, in which said inert gas is nitrogen.

16. A process according to one of claims 10 to 15, in which the content of oxygen in the mixture is kept not higher than 1 p.p.m.

17. A process according to claim 16, in which said content of oxygen is not higher than 0.5 p.p.m.

INTERNATIONAL SEARCH REPORT

national Application No

PCT/EP 98/03004

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/05 A61K9/107 A61K47/24 A61K47/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| Y | WO 97 10814 A (VESIFACT AG) 27 March 1997 cited in the application see the whole document --- | 1-17 |
| Y | EP 0 280 887 A (F. HOFFMANN-LA ROCHE & CO. AKTIENGESSELLSCHAFT) 7 September 1988 cited in the application see the whole document --- | 1-17 |
| Y | DE 32 21 579 A (ECKERT ET AL.) 22 December 1983 see the whole document --- | 1-8 |
| Y | FR 2 265 357 A (IMPERIAL CHEMICAL INDUSTRIES LIMITED) 24 October 1975 see the whole document & US 4 798 846 A cited in the application --- | 1-8 |
| -/-- | | |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

13 October 1998

Date of mailing of the international search report

21/10/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Benz, K

INTERNATIONAL SEARCH REPORT

national Application No
PCT/EP 98/03004

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|--|---|-----------------------|
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| Y | GB 2 298 789 A (ZENECA LIMITED) 18 September 1996 cited in the application see the whole document --- | 1-17 |
| A | DE 10 89 510 B (DR. RUDOLF REISS, CHEMISCHE WERKE) 22 September 1960 see the whole document --- | 1-8 |
| P, Y | US 5 637 625 A (HAYNES) 10 June 1997 see the whole document ----- | 1-17 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

national Application No

PCT/EP 98/03004

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|----------------------------|---------------------|
| WO 9710814 | A | 27-03-1997 | AU 6708096 A | 09-04-1997 |
| EP 280887 | A | 07-09-1988 | AU 599198 B | 12-07-1990 |
| | | | AU 1076688 A | 04-08-1988 |
| | | | CA 1319886 A | 06-07-1993 |
| | | | DE 3867502 A | 20-02-1992 |
| | | | DK 4088 A | 04-08-1988 |
| | | | IE 61068 B | 21-09-1994 |
| | | | JP 2645427 B | 25-08-1997 |
| | | | JP 63201133 A | 19-08-1988 |
| | | | US 4882164 A | 21-11-1989 |
| | | | ZA 8800562 A | 03-08-1988 |
| DE 3221579 | A | 22-12-1983 | NONE | |
| FR 2265357 | A | 24-10-1975 | GB 1472793 A | 04-05-1977 |
| | | | AU 502164 B | 12-07-1979 |
| | | | AU 7953675 A | 30-09-1976 |
| | | | BE 827290 A | 29-09-1975 |
| | | | CA 1038764 A | 19-09-1978 |
| | | | DE 2513797 A | 09-10-1975 |
| | | | DK 128675 A | 29-09-1975 |
| | | | FI 750941 A | 29-09-1975 |
| | | | HK 34380 A | 01-07-1980 |
| | | | IE 40839 B | 29-08-1979 |
| | | | JP 50154410 A | 12-12-1975 |
| | | | KE 3052 A | 27-06-1980 |
| | | | NL 7503696 A,C | 30-09-1975 |
| | | | SE 7503542 A | 29-09-1975 |
| | | | US 4798846 A | 17-01-1989 |
| | | | US 4056635 A | 01-11-1977 |
| | | | US 4452817 A | 05-06-1984 |
| | | | ZA 7501806 A | 25-02-1976 |
| GB 2298789 | A | 18-09-1996 | BR 9510452 A | 19-05-1998 |
| | | | DE 19509828 A | 19-09-1996 |
| | | | FR 2731617 A | 20-09-1996 |
| | | | WO 9629064 A | 26-09-1996 |
| | | | AU 1898895 A | 08-10-1996 |
| | | | CZ 9702904 A | 17-12-1997 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

national Application No

PCT/EP 98/03004

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| GB 2298789 A | | DK 106697 A | 17-09-1997 |
| | | EP 0814787 A | 07-01-1998 |
| | | FI 973702 A | 16-09-1997 |
| | | IT MI950529 A | 22-09-1995 |
| | | LU 90136 A | 27-11-1997 |
| | | NO 974278 A | 16-09-1997 |
| | | PL 322278 A | 19-01-1998 |
| | | SE 9703274 A | 10-09-1997 |
| | | SK 124797 A | 14-01-1998 |
| | | US 5714520 A | 03-02-1998 |
| | | US 5731355 A | 24-03-1998 |
| | | US 5731356 A | 24-03-1998 |
| DE 1089510 B | | NONE | |
| US 5637625 A | 10-06-1997 | AU 2329297 A | 10-10-1997 |
| | | EP 0796616 A | 24-09-1997 |
| | | WO 9734588 A | 25-09-1997 |